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MEETING REPORT

Nutrigenomics and gut health: meeting report from an international conference in Auckland, New Zealand, April 30, May 1–3, 2006

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Introduction

Nutrigenomics New Zealand (NuNZ) is a partnership among a major New Zealand University, The University of Auckland, and three crown research institutes, Crop & Food Research, AgResearch and HortResearch. It is the first nutrigenomics centre in New Zealand and has a website, http://www.nutrigenomics.org.nz. An initial 6 years of funding is provided through the New Zealand Foundation for Research Science and technology (FRST). The title of the project is "Tailoring New Zealand foods to match people's genes", and it involves six different sites across New Zealand, interacting to provide a strong focus on a single target outcome. The initial focus is on inflammatory bowel disease (IBD), especially one subset of such individuals who show the symptoms of Crohn's disease (CD). This is a good example of a disease where there is clear evidence for genetic predisposition, at least in a proportion of cases, but where environmental factors including diet, are likely to trigger symptoms of the disease. Unlike the situation in celiac disease, there is no single type of food which is either beneficial or detrimental. Thus the prospects are good for tailoring foods and/or diets to individual genotypes. Some of the results already obtained by NuNZ are relevant to gut health generally, and it is likely that pathway specific foods can be developed based upon current knowledge. To the best of our knowledge, NuNZ is the first strategic project centred on nutrigenomics, that brings together academic institutions and food industry to promote the study of nutrient-gene interactions, with the intention of developing foods and/or diets suited to specific genotypes. Thus, NuNZ was in a good position to host an international conference on "Nutrigenomics and Gut health".

The first international conference on Nutrigenomics and Gut Health brought together more than 200 individuals from 19 different countries. The topic reflected a growing recognition that gut health is crucial to overall health, and a key focus of the functional foods area. Gut health is heavily influenced by genetic polymorphisms, and also by the gut bacteria. The interplay between these and our diet provides a key not only to gut health, but also to an understanding of susceptibility to some key diseases of the Western world.

Technologies for nutrigenomics research

Two pre-conference workshops were held in order to explain concepts and terminology, and showcase new developments. These featured a range of scientists doing basic and applied research on genetics, bioinformatics, molecular biology, transcriptomics, proteomics and metabolomics. The first of these workshops, on the design and analysis of studies in genetic epidemiology, was organised and chaired by Chris Triggs and Mik Black (both from The University of Auckland). The lead speaker was Charles Cantor, Boston University, MA, USA, on the topic "Design and analysis of whole genome genetic scans". Charles provided a critical

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overview of technologies critical to characterising single nucleotide polymorphisms (SNPs), recognised as providing around 90% of the variation between individuals. He also alerted the audience to the growing understanding of the significance of gene copy number, and other variations in chromosome structure that are not well served by current methodologies. He explained how mass spectrometric methods can be applied to transcriptomics. While much of Charles' focus was on the techniques that are increasingly being applied and necessary equipment, he also discussed elements of experimental design. Brian Browning (University of Auckland, New Zealand) provided a statistician's perspective on "Design and analysis of studies in genetic epidemiology", while Mik Black (University of Auckland, New Zealand) covered "Microarray design and analysis". The final three talks in this session focussed attention on the challenges of working with multiple different systems across a wide range of groups, either within a single country or across international borders. Grier Page (University of Alabama, AL, USA) discussed how to apply statistics to high dimensional systems, Pieter Demmers (Crop & Food Research, New Zealand) provided a view on "Data warehousing and management in a cross-disciplinary consortium", while Jim Kaput (University of California, Davis, CA, USA) spoke on "Systems biology—integrating data from different disciplines in nutrigenomics—the International effort". The fruits of Jim's labours, and also the projects he discussed in this talk, can be found on the NuGO website (http://www.nugo.org/).

The second workshop was a more general one, entitled "Integrating new technologies in nutrigenomics", chaired and coordinated by William Laing (HortResearch). Key companies involved in the afternoon's session were Affymetrix (Rob Henke), and Invitrogen (Ben Huang). Rob emphasised new developments in tiling methodologies for epigenetic (methylation) and genetic characterisation of DNA samples. He stressed the importance of SNP chips, that can now characterise 500,000 or more SNPs in a single experiment. The companies involved in these are increasingly validating their use, and reducing costs to a reasonable extent. The Invitrogen speaker, Ben Huang, confessed to a growing concern that proteomics has not been developed to the same extent as transcriptomics, and described the proteomics chips that are now being picked up for a range of uses.

Other contributors to this session included four speakers from Nutrigenomics New Zealand—Martin Philpott (The University of Auckland) "Investigating nutrient—gene interactions in cell culture models", Matthew Barnett (AgResearch) "Animal models, microarrays and transcriptomics", William Laing (HortResearch) "Proteomics" and Daryl Rowan (HortResearch) "Metabolomics: applications in New Zealand".

The pre-conference workshop also provided an opportunity for young scientists to showcase their work. The impressive number of high quality presentations presented the judges with a different set of choices. Thus, in the end, the NuNZ and Agilent Best Oral Presentation prize was split between Simon Hughes (University of Reading) and Todor Arsov (Australian National University), while the Best Poster award went to Rachel Anderson (AgResearch)

Gene–diet interactions

Many of the sessions highlighted the continuous progress being made in the application of new genomic technologies to the field of nutrition. For many years, genetic studies of human disease, were limited to the investigation of so-called simple or Mendelian disease, that tended to be rare, severe and occurred with clear patterns of inheritance. Joes Ordovas (Tufts University, USA) described how the advent of the human genome project, and the development and use of common genetic markers known as single nucleotide polymorphisms (or SNPs), now ables us to make predictions about common disease and identify several contributing genetic elements that increase the risk or likelihood of developing disease. Charles Cantor (Sequenom) described how Sequenom have developed a genotyping platform with ability to screen large numbers of SNPs quickly and cheaply, has meant that it has now become possible to screen large numbers of individuals in a single study. For nutrigenomics, John Hesketh (University of Newcastle-Upon-Tyne, UK) and Andrew Shelling (University of Auckland) described how the field has developed to determine whether individuals with specific genotypes may benefit from eating certain foods or food components, and thereby improve their health and well-being.

While gene mutations or SNPs may contribute to the development of disease, there is now growing awareness than epigenetic mechanisms, which are changes in gene function that occur without a change in the DNA sequence, may also be important in the development of disease. Methylation of DNA sequences is the best example of an epigenetic change to the DNA sequence, as described by Lynn Ferguson (University of Auckland, New Zealand), Marie Dziadek (Garvan Institute, Australia) and Michael Fenech (CSIRO, Australia). Other genetic variations include copy number variants, which are simply the repetition of a part of the genome, that leads to changes in the level of expression of nearby genes. It is clear that the genome is more complex than we ever expected, and genes can be regulated in many ways, not just by simple gene mutations. In addition, there is now an understanding that nutrients may influence gene expression by affecting the methylation status of various genes, leading to altered risk of diseases in adulthood.

Ben van Ommen (NUGO, Netherlands) suggested that the steady development of knowledge generated from the human genome and biology has now merged in the field of systems biology, which allows the modeling and prediction of relevant biological processes. For nutrigenomics, there is now widespread investigation of diet-gene interactions, using a variety of 'omic technologies (Helen Kim, University of Alabama). However, concern was raised by Stephen Barnes (University of Alabama) about the limitations of some of this technology. Central to nutrigenomics is the study of the gut; requiring the study of interactions between nutrients, the microbiota, the epithelium and the immune system. While whole body investigation of humans is difficult, model systems can investigate defined aspects of the gut system. Nutrient-gene interactions with the immune system can be investigated using cell line models of human disease as described by Margot Skinner (HortResearch), while animal models using specific gene knockouts can provide more physiological understanding of disease (Nicole Roy, AgResearch). While all model systems have limitations, they all offer valuable insight into the human condition, and provide the opportunity to investigate the potential for individualised therapies for nutritional disorders.

Gene–diet–bacteria interactions

The human gastrointestinal tract, with a surface area of 400 m^2, is the largest interface between man and his environment (cf. skin 2 m^2; lung 100 m^2). The gastrointestinal barrier is a complex cellular structure, made up of four main components, which collectively act as a *biological bouncer* to protect the body from the entry of bacteria and antigens. The first are the intestinal epithelial cells that form a physical barrier consisting of intercellular junction complexes composed of tight junctions, adherens and desmosomes. The second component is the mucus layer produced by goblet cells, which forms a chemical barrier covering the epithelium. The third component, the immunological barrier, is regulated by immune cells that deliver pathogens to the mucosal lymphoid tissue and dendritic cells that extend their *arms* through the tight junctions to capture luminal antigens directly. The fourth component, the microbiological barrier, consists of the commensal bacteria that limit the colonisation of pathogens by competitively binding to the epithelium, competing for nutrients and producing antimicrobial compounds. How these components interact to maintain the gastrointestinal tract is fundamental to the delicate balance between health and disease.

From Gerald Tannock (University of Otago) we heard that the human gastrointestinal tract is inhabited by 10^{13} microbes—more than 10 times the number of cells that make up the human body—with representatives from 500 to 1,000 species. In adults, strict anaerobes outnumber facultative anaerobes by a factor of 100 to 1,000, so these are likely to have a profound influence on the function of the gastrointestinal tract. The identity of almost all of these microbes and their mechanism(s) of action remains largely unknown due to the difficulties culturing them. From Denise Kelly (Rowett Research Institute) we heard about the importance of commensal bacteria to the host. It has been illustrated in a number of germ-free mouse experiments, for example, that such mice required a higher calorific intake to maintain their weight and also had less developed immune systems (i.e. less circulating immunoglobulin, less T cells, etc.) than conventional mice. Colonisation of these animals by the commensal bacterium *Bacteroides thetaiotaomicron* assisted with the correct development of these processes by modulating the expression of host genes involved in nutrient absorption, glucose and fat metabolism and immune responses. Colonisation by other commensal bacteria shaped the immunity and maturation of the intestinal tract and molecules produced by the bacteria are believed to play a key role.

Although the interactions between intestinal cells and pathogenic bacteria are partially understood, their interactions with commensal bacteria have been poorly described. In reponse to pathogens, intestinal epithelial cells signal dendritic cells, which are normally loosely attached to the basal epithelium, to unzip tight junctions by destabilising them; the intestinal epithelial cells then form new tight junctions with the infiltrating dendritic cells. This enables dendritic cells to capture the intruding pathogens and transport them to the lymph nodes for induction of systemic immune responses. Commensal bacteria are also recognised by the dendritic cells, but they do not trigger this immune response. How this discrimination occurs is unclear. There is evidence that molecules secreted by intestinal epithelium cells control dendritic cell activation and thereby regulate tight junction integrity. Dirk Haller (Technical University of Munich) provided evidence that intestinal epithelial cell signalling and host-derived regulators, along with enteric bacteria are critical components of chronic intestinal inflammation. This points to a sophisticated communication network between commensal bacteria and intestinal cells, but little is known about this dialog.

The gastrointestinal tract is not a passive fermentation vessel, but is in a state of active intercommunication with its resident microbial ecosystem and our environment. We can not forget that perhaps one of the most important environmental factors that influence this interaction is our diet. From Richard Head (CSIRO Preventative Health Flagship) we heard about the importance of microbial fermentation of resistant starch in the colon, the possible

regulatory roles of products of that fermentation and implications for apoptosis and colorectal cancer.

We have only begun to understand the delicate balance between commensal bacteria, the gastrointestinal tract they inhabit and our health verses disease, let alone between health and optimal wellness. It becomes apparent that we need to identify both our allies and potential foes in order to exploit this diverse ecosystem, and to understand how our diet interacts with two genomes; the microbial and human for our benefit or otherwise.

Bringing nutritional genomics to the public and to industry

The third day of the conference covered the wide range of aspects related to bringing the concept of nutritional genomics to the reality of commercial personalised products, in particular food products. Lynn Ferguson (University of Auckland) provided an introduction to nutrigenomics for the food industry. She stressed the key principles, technologies and applications. She also focussed on the name. "Nutrigenomics" scares the public and the food industry, who are confusing it with genetic modification. While "personalised nutrition" may have been thought to be less threatening, in some ways this is even more challenging to the food industry, since it implies that they might need 4 million different products for the 4 million inhabitants of this country. "Targeted nutrition" has been suggested by industry as a more appealing compromise, since it suggests a limited number of high value products that could be developed for individuals and for population subgroups

Other presentions in this session covered the breadth of considerations required to bring nutrigenomic principles into the food industry. Don Love (University of Auckland) discussed the need for biomarkers to be used to validate the efficacy of foods, while Lyn Bridger (New Zealand Trade and Enterprise) talked about the national and international perspectives in bringing biotechnology foods to the market. This was followed with presentations discussing the prospects and technological challenges of making the leap to personalised food products from activities seen in model systems. Kevin Davies (Crop & Food) discussed manipulating nutrients for specific human purposes, while Kevin Sutton (Crop & Food) emphasised the challenges to food technology in developing personalised foods. The choice of ingredients, their presentation in foods, the requirement to retain bioactivity while maintaining an appealing taste and flavour, and how to monitor any claimed bioactivity were all discussion points.

The second session covered the ethical and public health issues surrounding the manufacture, marketing and sale of personalised food products based on nutrigenomic principals. David Castle (University of Guelph) and Nola Ries (University of Alberta) provided an international, and Donald Evans (University of Otago), a New Zealand perspective, on the ethics of personalised nutrition. They emphasised the current confusion in the minds of the public, and the need to provide reassurance before embarking further in this area. There was the well recognised concern about wide public genetic screening and the uses, and abuses, inherent in the production of such knowledge. There was also the issue of priority setting for production, and whether the prime driver should be determined by commercial profit margin or by public health need. The need for consideration of ethnic diversity, not just in genetics but also in perception, was raised. There is public confusion with the perception that nutrigenomics, genetic engineering and transgenics are somehow related.

The final session was focused on the commercial end products of nutrigenomics research, genetic health risk consultancies and personalised food products, their production, marketing, promotion and regulation. Four industry representatives provided different viewpoints. Jim Kaput (Nutragenomics) presented on "Nutrigenomics and the foods industry"; Rosalyn Gill-Garrison (Sciona) provided a "Consumer perspective: experience of a company specialising in nutrigenomics"; Mike Boland (Fonterra) discussed the logistics of how to develop and market customised food, while Tony Nowell (CEO, Griffins Foods) discussed issues for the New Zealand food industry with nutrigenomic foods. The marketing of advice based on what some saw as incomplete information generated a range of views. The potential for abuse by unethical marketers was seen as a big risk, but that exists even without nutrigenomics. Food industry speakers covered the need for profitability for any food product, although the potential of high-value niche marketing was seen as a positive.

The final two talks were provided by Bob Boyd and Dean Stockwell, from FSANZ (Food Safety Authority of Australia and New Zealand). Both talks were presented by the latter speaker, and covered regulatory issues with nutrigenomics foods. The potential impact of food regulations in either adding substantial extra costs to the definition and production of nutrigenomic foods was a salutary final message to conference attendees. The conference ended with a panel debate which emphasised the issues of bringing these foods to the public. There was a perceived need for genetic counseling—but a recognised dearth of people who possess such skills.

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